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Fast interaction between AMPA and NMDA receptors by intracellular calcium

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ABSTRACT

Suppression of NMDA receptor (NMDAR)-mediated currents by intracellular Ca^{2+} has been described as a negative feedback loop in NMDAR modulation. In the time scale of tenths of milliseconds the depth of the suppression does not depend on the Ca^{2+} source. It may be caused by Ca^{2+} influx through voltage-gated calcium channels, NMDAR channels or release from intracellular stores. However, NMDARs are often co-expressed in synapses with Ca^{2+}-permeable AMPA receptors (AMPARs). Due to significant differences in activation kinetics between these two types of glutamate receptors (GluRs), Ca^{2+} entry through AMPARs precedes full activation of NMDARs, and therefore, might have an impact on the amplitude of NMDAR-mediated currents. The study of Ca^{2+}-mediated crosstalk between AMPAR and NMDAR in native synapses is challenging due to high NMDAR Ca^{2+} permeability. Therefore, recombinant Ca^{2+}-permeable AMPAR and Ca^{2+}-impermeable NMDAR mutant channels were co-expressed in HEK 293 cells to examine their interaction. An AMPAR-mediated increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) reversibly reduced the size of NMDAR-mediated whole-cell currents. The time course of the NMDAR channel inactivation and recovery from inactivation followed the time course of the $[Ca^{2+}]_i$ transient. When brief (1 ms) pulses of glutamate were applied to outside-out patches, the degree of NMDAR inactivation increased with the increase in charge carried by the currents through co-activated AMPARs. However, AMPAR-mediated NMDAR inactivation was abolished in the presence of intracellular fast Ca^{2+} buffer BAPTA or in Ca^{2+}-free extracellular solution. We conclude that Ca^{2+} entering through AMPARs inactivates co-localized NMDARs in the time range of excitatory postsynaptic currents.

1. Introduction

At many excitatory synapses in the mammalian central nervous system (CNS), fast synaptic transmission is mediated by α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate receptors (AMPARs) and N-methyl-D-aspartate receptors (NMDARs) co-localized in the postsynaptic membrane [1] and co-activated simultaneously by the same neurotransmitter, L-glutamate. Their close proximity in the postsynaptic density allows ionotropic and non-ionotropic crosstalk between these receptors. NMDAR channels are highly permeable to Ca^{2+} [2] and contribute to the synaptically evoked elevation of Ca^{2+} in dendritic spines [3–5]. An increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) causes a reversible Ca^{2+}-induced inactivation of NMDAR-activated currents, irrespective of the sources of the $[Ca^{2+}]_i$ elevation [6–9]. We have shown recently that the Ca^{2+} influx during unitary NMDAR-mediated synaptic events is sufficient to produce detectable self-inhibition of NMDARs on a time scale of a few milliseconds [10].

AMPAR-mediated Ca^{2+} inflow varies for different classes of neurons depending on the subunit composition in a particular cell type [11]. Although most of the AMPAR channels expressed in the principal neurons have low Ca^{2+} permeability [12] there is still a detectable fraction of GluA2-lacking AMPARs in CA1 pyramidal neurons [13]. Besides these Ca^{2+}-permeable AMPARs have been suggested to be involved in LTP induction [14]. Furthermore, in fast spiking interneurons and in some other cell types AMPARs have a relatively high Ca^{2+} permeability [15] and are co-localized with NMDAR [6;16]. Moreover, simulations of a dual-component conductance produced by a brief glutamate pulse in fast spiking basket

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